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LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI,
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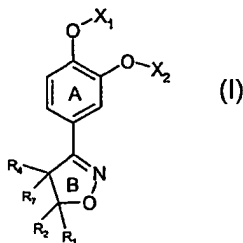
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ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: CONDENSED ISOXALINE DERIVATIVES AS INHIBITORS OF PHOSPHODIESTERASE TYPE-IV


(57) Abstract: The present invention relates to isoxazoline derivatives of formula (I), which
can be used as selective inhibitors of phosphodiesterase (PDE) type IV. In particular, com-
pounds disclosed herein can be useful in the treatment of AIDS, asthma, arthritis, bronchitis,
chronic obstructive pulmonary disease (COPD), psoriasis, allergic rhinitis, shock, atopic der-
matitis, Crohn's disease, adult respiratory distress syndrome (ARDS), eosinophilic granuloma,
allergic conjunctivitis, osteoarthritis, ulcerative colitis and other inflammatory diseases in a
patient, particularly in humans. The present invention also relates to processes for the prepa-
ration of disclosed compounds, as well as pharmaceutical compositions thereof, and their use
as phosphodiesterase (PDE) type IV inhibitors.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

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 A61P11/00 A61P31/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	<p>WO 2005/021515 A (RANBAXY LABORATORIES LIMITED; PALLE, VENKATA, P; BALACHANDRAN, SARALA;) 10 March 2005 (2005-03-10)</p> <p>claim 1</p> <p>page 39 - page 45</p> <p>page 47 - page 50</p> <p>examples</p> <p style="text-align: center;">----- -/-</p>	1-29

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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- * & * document member of the same patent family

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INTERNATIONAL SEARCH REPORT

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; DAS, BISWANATH ET AL: "Synthetic studies on natural products. Part 20. Synthesis of novel spiro-2-isoxazolines derived from parthenin" XP002380558 retrieved from STN Database accession no. 2005:1160450 compounds with RN 882164-94-5, 882164-95-6, 882164-99-0, 882165-00-6 abstract & INDIAN JOURNAL OF CHEMISTRY, SECTION B: ORGANIC CHEMISTRY INCLUDING MEDICINAL CHEMISTRY, 44B(10), 2149-2151 CODEN: IJSBDB; ISSN: 0376-4699, 2005,</p>	1,3
X	<p>WO 95/14680 A (PFIZER INC; KLEINMAN, EDWARD, F) 1 June 1995 (1995-06-01) claims page 21; example 27</p>	1-29
X	<p>FIHI R ET AL: "REACTION SES METHYLENE GAMMA-BUTYROLACTONES AVEC LES ARYLNITRILOXYDES. EVOLUTION INATTENDUE DU BISADDUIT ISSU DE LA 5-METHYLENE(5H)FURAN-2-ONE" BULLETIN DES SOCIETES CHIMIQUES BELGES, vol. 104, no. 1, 1995, pages 55-62, XP009044216 ISSN: 0037-9646 compound 6F</p>	1,3
X	<p>WO 95/14681 A (PFIZER INC; KLEINMAN, EDWARD, F) 1 June 1995 (1995-06-01) page 13; example 16 page 21; compound 21</p>	1-29
X	<p>FOS, EMPAR ET AL: "Synthesis of isomeric series of aryltetrahydrobenzoxazoles and arylcyclopentisoxazoles" JOURNAL OF HETEROCYCLIC CHEMISTRY, 29(1), 203-8 CODEN: JHTCAD; ISSN: 0022-152X, 1992, XP002393576 compounds 3C, 4C</p>	1,3

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INTERNATIONAL SEARCH REPORT

PCT/IB2006/000285

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KONOPIKOVA, M. ET AL: "1,3-Dipolar cycloadditions of heterocycles. XXIII. Cycloadditions of benzonitrile oxides to N-(2,6-dialkylphenyl)maleimides" XP002393583 retrieved from STN Database accession no. 1992:151622 compounds with RN 139395-56-5, 139395-65-6, 139395-74-4, 139395-77-0, 139395-67-1, 139395-70-6 abstract & CHEMICAL PAPERS , 45(6), 789-805 CODEN: CHPAEG; ISSN: 0366-6352, 1991,</p>	1,3
X	<p>DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; BRAHMESHWARI, G. ET AL: "Synthesis and biological activity of fused heterocycles derived from embelin" XP002393584 retrieved from STN Database accession no. 1991:228802 compounds with RN 133701-91-4, 133701-95-8, 133701-87-8 abstract & INDIAN JOURNAL OF CHEMISTRY, SECTION B: ORGANIC CHEMISTRY INCLUDING MEDICINAL CHEMISTRY , 30B(3), 369-70 CODEN: IJSBDB; ISSN: 0376-4699, 1991,</p>	1,3
X	<p>DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KUMAR, K. AJAY ET AL: "Synthesis of 3-aryl-5N-aryl-4,6-dioxo-pyrrolo[3,4-d]-7, 8- dihydroisoxazoles via 1,3-dipolar cycloaddition reaction" XP002393585 retrieved from STN Database accession no. 2001:302770 compounds with RN 348630-00-2 to 348630-06-8 abstract & INDIAN JOURNAL OF CHEMISTRY, SECTION B: ORGANIC CHEMISTRY INCLUDING MEDICINAL CHEMISTRY , 40B(4), 269-273 CODEN: IJSBDB; ISSN: 0376-4699, 2001,</p>	1,3

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INTERNATIONAL SEARCH REPORT

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SINGAL, K. K. ET AL: "1,3-Dipolar cycloaddition reactions of nitrile oxides with N-arylmaleimides leading to the synthesis of 3,5-diaryl-3a,4,6,6a- tetrahydro-4H,6H-pyrrolo[3,4-d]isoxazole-4 ,6-diones" XP002393586 retrieved from STN Database accession no. 2001:82529 compounds with RN 333404-83-4, 333404-89-0, 333404-93-6, 333405-03-1, 333404-97-0, 333405-03-1, 333405-08-6, 333405-13-3 abstract & CHEMICAL & ENVIRONMENTAL RESEARCH , 9(1 & 2), 47-53 CODEN: CEREEH; ISSN: 0971-2151, 2000,</p>	1,3
X	<p>DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; BRAHMESHWARI, G. ET AL: "Synthesis of 3-arylnaphth[2,3-d]isoxazole-4,9-diones from Lawsone" XP002393587 retrieved from STN Database accession no. 1995:333432 compounds with RN 161497-83-2, 161497-88-7 abstract & INDIAN JOURNAL OF CHEMISTRY, SECTION B: ORGANIC CHEMISTRY INCLUDING MEDICINAL CHEMISTRY , 34B(2), 139-40 CODEN: IJSBDB; ISSN: 0376-4699, 1995,</p>	1,3
X	<p>DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; HUANG, HAI-HONG ET AL: "Synthesis of chiral 5-1-menthyloxybutyrolacto[3,4-d]isoxazolin e derivatives" XP002393588 retrieved from STN Database accession no. 2003:951601 compounds with RN 476683-28-0, 561317-49-5 abstract & GAODENG XUEXIAO HUAXUE XUEBAO , 24(11), 2000-2004 CODEN: KTHPDM; ISSN: 0251-0790, 2003,</p>	1,3

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INTERNATIONAL SEARCH REPORT

PCT/IB2006/000285

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2 284 600 A (* SHELL INTERNATIONALE RESEARCH MAATSCHAPPIJ B.V) 14 June 1995 (1995-06-14) claim 11 example 17; table 1	1,3
X	SUBRAMANIAN T ET AL: "FACILE SYNTHESIS OF 3-AROYL-3-SULFOLENES THROUGH CYCLOADDITIONS OF ARYLNITRILE OXIDES & 3-SULFOLENE" SYNTHETIC COMMUNICATIONS, MARCEL DEKKER, INC., BASEL, CH, vol. 27, no. 15, 1997, pages 2557-2562, XP009041534 ISSN: 0039-7911 compounds 3D,3F	1,3
X	GABOURY J A ET AL: "Enantiocontrolled synthesis of burseran, brassilignan, dehydroxycubebin, and other tetrahydrofuran lignans in both enantiomeric forms. Application of intermolecular nitrile oxide cycloadditions and lipase-mediated kinetic resolutions" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 58, no. 8, 1993, pages 2173-2180, XP002330566 ISSN: 0022-3263 compounds 9C,9D	1,3
X	HASSIKOU A ET AL: "Synthèse de nouveaux polyhétérocycles" TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, NL, vol. 42, no. 34, 20 August 2001 (2001-08-20), pages 5857-5861, XP004295942 ISSN: 0040-4039 compound 16	1,3
X	SYASSI B ET AL: "Addition Dipolaire-1,3 des Arylnitriloxydes avec quelques Dipolarophiles Olefiniques sur Alumine en Milieu sec et sous Micro-ondes" TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, NL, vol. 38, no. 51, 22 December 1997 (1997-12-22), pages 8855-8858, XP004162383 ISSN: 0040-4039 compound 7H	1,3

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INTERNATIONAL SEARCH REPORT

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SYASSI B ET AL: "Short communication" TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, NL, vol. 40, no. 40, 1 October 1999 (1999-10-01), pages 7205-7209, XP004179018 ISSN: 0040-4039 compounds 4E,5E	1,3
X	SIBI M P ET AL: "SYNTHESIS OF LIGNAN NATURAL PRODUCTS (PLUS OR MINUS)DEHYDROXYCUBEIN AND (PLUS OR MINUS)BURSERAN BY INTERMOLECULAR NITRILE OXIDE CYCLOADDITION" SYNLETT, THIEME INTERNATIONAL, STUTTGART, DE, no. 1, January 1992 (1992-01), pages 83-84, XP001204506 ISSN: 0936-5214 compound 3	1,3
X	SALGADO-ZAMORA H ET AL: "OXIDATIVE DEGRADATION OF ARYLFURO-1,2-OXAZOLES TO ARYLNITRILES BY POTASSIUM PERMANGANATE" HETEROCYCLIC COMMUNICATIONS, FREUND PUBLISHING HOUSE, TEL AVIV, IL, vol. 7, no. 3, 2001, pages 209-212, XP009041526 ISSN: 0793-0283 compound 3A	1,3
X	TIAN L ET AL: "1,3-Dipolar cycloaddition reactions of nitrile oxides to prop-1-ene-1,3-sultone" JOURNAL OF HETEROCYCLIC CHEMISTRY, HETEROCORPORATION. PROVO, US, vol. 40, no. 6, 2003, pages 1071-1074, XP002330565 ISSN: 0022-152X compound 4L	1,3

INTERNATIONAL SEARCH REPORT

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Box II Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 4 and 5 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

International Application No. PCT/IB2006 /000285

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-5(part); 6-13;14(part); 15,19-29

Compounds of claim 1 in which R1 and R2 together form a ring (i. e. spirocondensed compounds), processes for their preparation (and for intermediates) and their use as PDE-IV inhibitors

2. claims: 1-5(part); 14(part), 17,18

Compounds of claim 1 in which R2 and R4 together form a ring (i. e. orthocondensed compounds), processes for their preparation and their use as PDE-IV inhibitors

INTERNATIONAL SEARCH REPORT

PCT/IB2006/000285

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